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None

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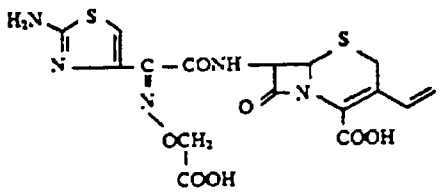
(54) Abstract Title
PREPARATION OF ORALLY ACTIVE CEPHALOSPORIN ANTIBIOTIC-CEFIXIM

(57) A process for the preparation of an orally active cephalosporin antibiotic-cefixim, of formula I in which an ester of formula II is reacted for 30 - 90 minutes at room temperature in an organic solvent with an aqueous solution of inorganic base in presence of a phase transfer catalyst, thus allowing that resultant mixture settles till separation of the aqueous and organic phases, isolating the cefixim of required purity from the aqueous layer by acidifying said aqueous layer by acidifying said aqueous layer.



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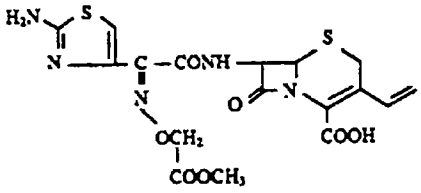

(II)

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DESCRIPTION

PROCESS FOR THE PREPARATION OF ORALLY ACTIVE CEPHALOSPORIN ANTIBIOTIC-CEFIXIM

This invention relates to a process for the preparation of orally active cephalosporin Antibiotic-Cefixim.

BACKGROUND

The first of a new series of cephalosporins which exhibit most of the properties desirable in a compound to be used for empiric therapy was Cefotaxime, a methoxy iminocephalosporin bearing a 2-iminothiazol-4-yl--group, which was swiftly followed by a number of very similar methoximes wih different 3-substituents like Ceftizoxime, Cefmenoxime, Ceftriaxone and Ceftazidime compound **(Am.J.Med. (1985), Suppl 2A,14.; Am.J.Med(1985), Suppl 2A,21.; Clin.Pharm.(1987), 6,59.; Recent Advances in the Chemistry of β-Lactam Antibiotics, Special publication No. 52, The Royal Society of Chemistry, London, July 1984, p.1).**

Most of the aminothiazolyl cephalosporins are not absorbed from the GI tract and are not orally active. Cefixim is one such exception having carboxymethoxime group with small lipophillic 3-substituents. In the synthesis of Cefixim, 3-acetoxy group of 7-ACA is transformed via a 3-phosphonium salt and by Wittig reaction to a vinyl intermediate, which is then converted into Cefixim of formula I by standard procedure as described in J.Antibiotics (1985), 38, 1738. The said standard process comprises of the following steps:

- hydrolysis of methyl ester of formula II with inorganic base in aqueous solution at 40 degree C for 7 hours;
- adjusting the pH of the resulting solution to 6.0 with 10% HCl and subjecting it to column chromatography on Diaion HP-20 for purification;
- eluting the column with water and acidifying the fraction containing the desired compound (Cefixim) to pH 2.1 with 10% HCl;
- stirring the resulting solution for one hour and collecting the precipitate of Cefixim by filtration.

The product yield in this process is 41%. This process suffers from the following drawbacks:

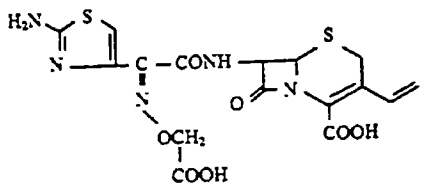
- The reaction is carried out at an elevated temperature, viz., 40 degree C and is completed in 7 hours. This leads to the formation of many undesirable impurities, and thereby decrease the purity of the final product in the solution.
- To get the desired purity of the final product, the said solution is subjected to column chromatography on Diaion HP -20 (Resin).
- The purification technique involve the use of column chromatography using Diaion HP -20 which is expensive and industrially uneconomical.

In US Patent 440924, Cefixim is obtained by hydrolysing tertiary butyl ester along with other protected substituents such as benzhydral and formamide by using trifluoroacetic acid. This process involves more number of complicated steps.

The objects of this invention are:

- To reduce the reaction time by increasing the speed of the reaction.

- To decrease the reaction temperature.
- To overcome the formation of undesirable impurities are increase the yield.
- To eliminate the use of expensive uneconomical purification technique and thereby decrease the production cost.
- To reduce the number of complicated steps in the process.



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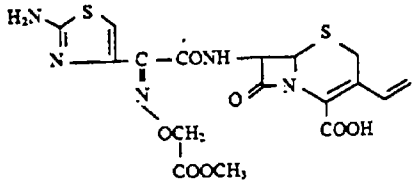

(II)

To achieve the aforesaid objectives this invention provides a process of preparing orally active cephalosporin antibiotic Cefixim of formula I comprising:

- reacting ester of formula II in organic solvent with aqueous solution of inorganic base in the presence of phase transfer catalyst at ambient temperature for a period of 30-90 minutes;
- allowing the resulting mixture to settle till the aqueous and organic layers separate;
- isolating Cefixim of required purity from aqueous layer by acidifying the said aqueous layer.

The ester of formula II, is a methyl ester and the orgsnic solvent is a halogenated aliphatic hydrocarbon preferably methylene chloride. The weak inorganic base used in the process is alkali carbonate preferably K_2CO_3. The ambient temperature during the reaction is preferably between 10 to 25

degree C and the acidification of the said aqueous layer is carried out by 10% HCl to pH 2.1. Phase transfer catalyst improves the reaction condition as well as the quality of the final product without using purification techniques. The phase transfer catalyst used in the process is quaternary ammionium salt(s) of general formula $R_4N^+X^-$,

where,

R = n-butyl $(CH_3(CH_2)_3^-)$,
= n-pentyl $(CH_3(CH_2)_4^-)$
= n-hexyl $(CH_3(CH_2)_5^-$

and X = Cl^-, Br^-, I^- or OH^-

The said quaternary ammonium salt is tetraalkylammonium halide or hydroxide. The cation contains large alkyl groups which confer upon its solubility in organic solvents. The anion is a halide or a hydroxide group, which is soluble in water. Such a cation will transport the anion (hydroxide ion) as its counter ion into organic phase from aqueous phase. This greatly facilitates the reaction which otherwise would occur only at the interphase

The invention will now be described with reference to the following examples:

EXAMPLE 1:-

K_2CO_3(166 mg, 1.2mmol) dissolved in water was added to a stirred solution of the ester of formula II (500 mg, 1.07 mmol) and tetrabutylammonium bromide (3.2 mg, 0.01 mmol) in CH_2Cl_2 at 20 degree C. The reaction was complete in 40 min. (HPLC monitoring). The pH of the aq. layer after separation was adjusted to 2.1 by 10% HCl to yield 286 mg of Cefixim of formula I. Tests were conducted on this compound of formula I by

standard methods and the results found were as follows:

Purity (HPLC) = 98.5%, $[\alpha]^{25}{}_{D}$ = -78.76°;

IR (Kbr) : 1771, 1669 cm^{-1};

^{1}H NMR (DMSO-d_6) : δ 3.55-3.88(2H,q,J = 17.66 Hz);

4.6 (2H,s); 5.21 (1H,d,J = 4.79 Hz); 5.32 (1H,d,J = 11.39 Hz);

5.6 (1H,d,J = 17.47 Hz); 5.81 (1H,dd,J = 4.78 Hz, 8.18 Hz);

6.81 (1H,s); 6.91 (1H,dd,J = 11.27 Hz, 17.52 Hz); 7.29 (2H,bs, D_2O exchangeable);

9.61 (1H,d,J = 8.2 Hz, D_2O exchangeable).

EXAMPLE 2:-

K_2CO_3 (166mg, 1.2mmol) dissolved in water was added to a stirred solution of the ester of formula II (500 mg, 1.07 mmol) and tetrahexylammonium chloride (3.9 mg, 0.01 mmol) in CH_2Cl_2 at 20 degree C. The reaction was complete in 75 min. (HPLC monitoring). The pH of the aq. layer after separation was adjusted to 2.1 by 10% HCl to yield 297 mg of Cefixim for formula I. Tests were conducted on this compound of formula I by standards methods and results found were as follows:

Purity (HPLC) = 98.7%; $[\alpha]^{25}{}_{D}$ = -79.52°;

IR (KBr) = 1769, 1670 cm^{-1};

^{1}H NMR (DMSO-d_6): δ 3.54-3.88(2H,q,J = 17.5 Hz); 4.59 (2H,s);

5.21 (1H,d,J = 4.76 Hz); 5.32 (1H,d,J =17.36 Hz); 5.6 (1H,d,J = 17.48 Hz);

7.30 (2H,bs, D_2O exchangeable); 9.60 (1H,d,J = 8.15 Hz, D_2O exhangeable).

CLAIMS

1. A process of preparing orally active cephalosporin antibiotic - Cefixim of formula I comprising:

- reacting ester of formula II in organic solvent with aqueous solution of inorganic base in the presence of a phase transfer catalyst at ambient temperature for a period of 30-90 minutes;
- allowing the resulting mixture to settle till the aqueous and organic layers separate;
- isolating the Cefixim of required purity from aqueous layer by acidifying the said aqueous layer.

2. A process as claimed in claim 1 wherein the said ester of formula II is a methyl ester.

3. A process as claimed in claim 1 wherein the weak inorganic base is alkali carbonate preferably K_2CO_3.

4. A process as claimed in claim 1 wherein the organic solvent is a halogenated aliphatic hydrocarbon.

5. A process as claimed in claim 4 wherein the said halogenated aliphatic hydrocarbon is methylene chloride.

6. A process as claimed in claim 1 wherein the ambient temperature during the reaction is between 10-25 degree C.

7. A process as claimed in claim 1 wherein acidification of the aqueous layer is carried out by 10% HCl to pH 2.1.

8. A process a claimed in claim 1 wherein the said phase transfer catalyst is quaternary ammonium salts of geneal formula $R_4N^+ X^-$

where,

R = n-butyl $(CH_3(CH_2)_3^-)$,
= n-pentyl $(CH_3(CH_2)_4^-)$,
= n-hexyl $(CH_3(CH_2)_5^-)$,

and X = Cl^-, Br^-, I^- or OH^-.

9. A process as claimed in claim 8 wherein the phase transfer catalyst is tetra-butylammonium bromide or tetrahexylammonium chloride.

10. A process as claimed in claim 1 substantially as described in Example 1 or Example 2.

11. An oral pharmaceutical composition comprising an orally active cephalosporin antibiotic - cefixim when prepared by a process as claimed in any one of the preceding claims.

The Patent Office

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Application No: GB 9821967.8
Claims searched: 1-11

Examiner: S.I.Ahmad
Date of search: 10 December 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C(CKE, CPK)

Int Cl (Ed.6): C07D-501/22

Other: Data-base: Cass-on -line

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	No relevant document	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.